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EXAMINER	
CROW, ROBERT THOMAS	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

Office Action Summary	Application No.	Applicant(s)	
	10/813,467	PECK ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 27 June 2008 in which claims 1 and 56 were amended, no claims were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 28-59 and 61 are under prosecution.

Interview Summary

2. The interview summary is acknowledged. However, Applicant has improperly characterized the statements made by the examiner during the interview. The examiner did not explicitly state that language excluding the "1 to 1" flow through embodiment in Schleifer B would appear tot overcome the rejections of record. In addition, Interview Summary mailed 1 April 2008 clearly indicates that agreement with respect to the claims was not applicable.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 28-36, 38-44, 46-47, 49-50, 54-59, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) in view of Anderson et al (U.S. Patent No 5,186,824, issued 16 February 1993) as evidenced by the online dictionary at dictionary.cambridge.org and, as applied to claim 34, as evidenced by the online dictionary at Merriam-webster.com.

Regarding claim 28, Gamble et al teach a method of synthesizing an addressable array of nucleic acid molecules on a substrate. In a single exemplary embodiment, Gamble et al teach a substrate upon which micro-sized spots of reagents are dispensed in particular locations (column 3, lines 35-45). The reagents are removable from the substrate surface (column 2, lines 45-50), and thus are attached to the surface. The reagents are phosphoramidites (column 2, lines 13-16), which are blocked nucleoside monomers in accordance with the example presented in the first paragraph on page 15 of the instant specification. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "blocked nucleoside monomer" (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]). Because the spotted blocked nucleoside monomers are localized onto specific locations on the substrate (column 2, lines 15-25), and because the locations are predetermined by a used prior to synthesis of the array (column 2, lines 39-45), the array is an addressable array in accordance with the example presented on page 10 of the instant specification. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding an "addressable array."

Gamble et al teach additional reagents are transported to a reaction chamber which contacts the substrate, wherein the additional reagents include deprotecting reagents (column 4, lines 35-45). The deprotecting reagent is a

deblocking agent because it removes a trityl protecting group that blocks further synthesis on the nucleoside monomer (column 12, lines 59-67).

Gamble et al also teach the deblocking fluid is then displaced from the surface of the substrate, which now comprises attached unblocked nucleoside monomers, using a purging fluid in the form of a wash fluid used between synthesis steps (column 10, lines 15-25). Gamble et al also teach the attached unblocked nucleoside on the surface is then reacted with another blocked nucleoside monomer to produce the addressable array of nucleic acid molecules on the surface; namely, the next blocked phosphoramidite molecule is applied to the substrate after the substrate is oriented with away from the reaction chamber and towards a jetting system that jets a phosphoramidite at selected loci (i.e., on the array (column 15, line 50-column 16, line 5 and column 3, lines 35-45).

It is noted that while the claim is drawn to contacting "an" entire surface of said substrate," the claim does not specifically require contacting **the** entire surface of the substrate. Thus, the claim encompasses contacting only a portion of the entire surface of the substrate; namely, only the portion having the blocked monomers or polymers.

Gamble et al teach the addition of reagents to the surface of the substrate that is sealed in a reaction chamber in several different configurations.

In a first embodiment, the substrate is sealed in a reaction chamber in which reagents flow over and immerse the substrate (column 3, lines 35-60), such that the entire surface of the substrate is uniformly covered with reagents (column 6, lines 35-40). The online dictionary at dictionary.cambridge.org

defines "immerse" as "to put something or someone completely under the surface of a liquid." Thus, "immersion" of the substrate contacts the entire surface of the substrate with reagents. Thus, Gamble et al clearly suggest uniformly covering (i.e., contacting) the entire surface of the substrate with reagents (column 6, lines 35-40).

In a second embodiment, Gamble et al also teach Figures 4a-c and 5, which show substrate 20 pressed against chamber 26 and against seal 28, which defines the surface of the substrate subjected to the fluid treatments (column 6, lines 30-45 and column 7, lines 25-40).

In a third embodiment, Gamble et al teach single array 66, which comprises a plurality of blocked phosphoramidites (column 2, lines 13-50), is pressed against the seal and subjected to reagent flow (i.e., a reagent stream; Figure 4c and column 7, lines 1-20).

Thus, in comparing the second embodiment of Figure 4a to the third embodiment of Figure 4c, it is clear that Figure 4a encompasses containing all of the spots on the array within seal 28 so that the entire surface of the substrate that comprises the monomers is contacted with the reagents flowed through the reaction chamber.

Alternatively, Figure 4c clearly indicates that at least one array, which is the entire surface of the substrate comprising the blocked monomers, is within seal 28 so that the entire surface of the substrate that comprises the monomers is contacted with the reagents flowed through the reaction chamber. The

additional arrays 66 of Figure 4c are other structures encompassed by the open claim language "comprising" of the instant claims.

In addition, it is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories,* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC,* 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component); Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). Thus, the teaching of Gamble et al that an individual array within a plurality of arrays **may** be sealed against the reaction chamber separately (column 7, lines 1-15) encompasses the alternate embodiment wherein the individual arrays are **not** separately sealed against the chamber; i.e., all of the arrays are sealed against the chamber at the same time (compare Figures 4a and 4c). See MPEP § 2123 [R-5].

Therefore, in each of the embodiments detailed above, the portion of substrate 20 contained within seal 28 is interpreted as "an entire surface of the substrate," and because the entire surface of the substrate within seal 28 is

contacted with the reagents as described below, Gamble et al teach contacting "an" entire surface of said substrate with reagents as required by the claim.

While Gamble et al teach the substrate is placed in a reaction chamber wherein reagents flow over and immerse the substrate (column 3, line 45-column 4, line 5), and that the reagents include phosphoramidites (i.e., blocked nucleoside monomers), wash reagents, deprotection (i.e. deblocking) reagents, activation reagents, oxidation regents, and any other necessary synthesis reagents (column 4, lines 35-46), Gamble et al do not explicitly teach the wash reagent contact said entire surface of the substrate; i.e., that the wash solution flows through the same chamber.

However, Anderson et al teach a method for producing an array of oligonucleotides on a substrate, wherein a first nucleoside capped with a trityl group attached to the surface of a support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, a surface of the substrate (i.e., solid support) is exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20). Anderson et al also teach

increased washing efficiency and quantitative replacement of one reagent by the next is a fixed requirement for polymer synthesis on a surface (column 19, lines 25-40), and that extensive washing between use of reagents is necessary to ensure each reagent reacts properly so that the yield of the polymer is not diminished (column 3, lines 45-60). Anderson et al also teach the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract). Thus, Anderson et al teach the known technique of performing all of the fluid steps, including washing, with a single reaction chamber.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising steps including washing of the array substrate as taught by Gamble et al so that each previous reagent is quantitatively replaced by a washing fluid as taught by Anderson et al and so that the reaction chamber of Gamble et al is used as a single reaction chamber for all of the fluid manipulation steps as taught by Anderson et al arrive at the instantly claimed method with a reasonable expectation of success. Quantitative replacement of reagents on the surface of the support requires displacement of said reagent from the entire surface of the substrate via use of the washing fluid as taught by Anderson et al. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of ensuring that each reagent reacts properly so that the yield of the polymer is not diminished, thus meeting the fixed requirements of washing efficiency and

quantitative replacement of solutions during polymer synthesis as explicitly taught by Anderson et al (column 19, lines 25-40 and column 3, lines 45-60). The ordinary artisan would also have been motivated to use the single reaction chamber of Anderson et al as a single reaction chamber for all of the fluid steps in the method of Gamble et al because the use of a single reaction chamber for all of the fluid steps, including washing, would have resulted in a method having the additional added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow as explicitly taught by Anderson et al (Abstract). In addition, it would have been obvious to a person of ordinary skill in that art at the time the claimed invention was made that the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al could have been applied to the method of Gamble et al with predictably results because the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al predictably results in a reliable method of performing DNA synthesis steps.

Regarding claim 29, the method of claim 28 is discussed above. Anderson et al also teach a blocked nucleoside monomer is attached to the substrate by contacting the substrate with a fluid comprising a blocked nucleoside monomer at a location on the substrate that comprises hydroxy groups; namely, Anderson et al teach a general method for oligonucleotide synthesis, wherein the blocked monomer in step ii of Table I is added to the unblocked attached nucleotide of

step i, which has a free hydroxyl group at the 5' end generated by the detritylation step (column 19, line 40-column 20, line 50).

Therefore, it would have been obvious to the ordinary artisan at the time the claimed invention was made that the known general method of oligonucleotide synthesis of Anderson et al comprising the use of tritylated phosphoramidite monomer groups, deblocking fluids, and wash fluids of Anderson et al could have been applied in place of the synthesis method of Gamble et al, which also comprises the use of tritylated phosphoramidite monomer groups (column 2, lines 25-35), deblocking fluids, and wash fluids, with predictable results because the known general method of oligonucleotide synthesis of Anderson et al predictably results in the reliable synthesis of oligonucleotides on a solid support.

Regarding claim 30, the method of claim 28 is discussed above. Gamble et al teach the steps of the method are repeated a plurality of times; namely, the method synthesizes polymers (column 2, lines 39-47) of nucleotides (column 2, lines 13-16). Because oligonucleotide polymers have multiple nucleotides therein, the steps are repeated a plurality of times. Alternatively, Anderson et al also teach the steps are repeated a plurality of times (column 20, lines 2). Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the steps of the method are repeated a plurality of times.

Regarding claim 31, the method of claim 28 is discussed above. Gamble et al teach the substrate comprises a surface of a planar support; namely, the

support is a microscope slide (column 3, lines 5-10 and substrate 20 of Figure 1), which is planar because it is flat. Alternatively, Anderson et al also teach the substrate comprises a surface of a planar support; namely, the support is a flat disc (column 6, lines 49-56). Thus, modification of the method of Gamble et al with the teachings of Anderson et al a results in a method wherein the substrate comprises a surface of a planar support.

Regarding claim 32, the method of claim 28 is discussed above. Anderson et al also teach the displacing step causes minimal mixing of deblocking and purging fluids; namely, density differences are used to minimize mixing (column 10, lines 23-24). Thus, modification of the method of Gamble et al with the teachings of Anderson et al a results in a method wherein the displacing step causes minimal mixing of deblocking and purging fluids.

Regarding claim 34, the method of claim 28 is discussed above. Gamble et al also teach the substrate comprises a surface of a planar support; namely, the support is a microscope slide (column 3, lines 5-10 and substrate 20 of Figure 1), which is planar because it is flat. The surface is nascent because the surface is activated before synthesis (column 15, lines 50-55). Because the specification has no limiting definition of the word "nascent," the word is interpreted as "having recently come into existence" in accordance with the online dictionary at Merriam-webster.com.

Regarding claim 35, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid has a density that is different from the deblocking fluid; namely, the solid supports are exposed to reagents sequentially

wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D). Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the purging fluid has a density that is different from the deblocking fluid.

Regarding claims 36 and 38, the method of claim 28 is discussed above. Anderson et al also teach the deblocking fluid and the purging fluid have a density difference, expressed as the Atwood number, of 0.01 or more. In a single exemplary embodiment, Anderson et al teach the deblocking (detritylation) fluid has a density that is greater than that of methylene chloride (i.e., 1.325 g/mL; column 21, lines 1-10). Detritylation is followed with a wash using acetonitrile as a purging solution, which has a density of 0.714 g/mL (Table II, step 3). Calculating the density difference using pure methyl chloride results in an Atwood number of 0.2996; a higher density deblocking fluid gives a higher Atwood number. Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the deblocking fluid and the purging fluid have a density difference, expressed as the Atwood number, of 0.01 or more.

Regarding claim 39, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid is an organic fluid; namely, 50% dichloromethane and 50% dimethylformamide (Table II). Thus, modification of

the method of Gamble et al with the teachings of Anderson et al results in a method wherein the purging fluid is an organic fluid.

Regarding claim 40, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid comprises an oxidizing agent; namely, the purging fluid is interpreted to be all of the fluids of Table I following the deprotection step i (column 20), which are introduced in one long series of changing densities (column 7, lines 5-19). The series that makes up the purging fluid includes the oxidizing agent iodine (step iv of Table I). Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the purging fluid comprises an oxidizing agent.

Regarding claims 41 and 42, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid comprises a wash fluid; namely, step 3 of Table II is a washing step using 50% dichloromethane and 50% dimethylformamide (i.e., claim 17; Table II), which is an organic fluid (i.e., claim 18). Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the purging fluid comprises a wash fluid.

Regarding claim 43, the method of claim 41 is discussed above. Anderson et al also teach the wash fluid is acetonitrile (column 13, line 67-column 14, line 1). Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the wash fluid is acetonitrile.

Regarding claim 44, the method of claim 28 is discussed above. Anderson et al also teach the deblocking fluid is displaced with a purging fluid in a manner

that moves a stratified interface across the surface; namely, interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D). Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein a deblocking fluid is displaced with a purging fluid in a manner that moves a stratified interface across the surface.

Regarding claim 46, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid limits the efficiency of the deblocking fluid; namely, the deblocking reaction requires acid (e.g., dichloroacetic acid; step i of Table I). Addition of any washing fluid decreases the concentration of acid, thereby limiting the efficiency of deblocking. Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the purging fluid limits the efficiency of the deblocking fluid.

Regarding claim 47, the method of claim 29 is discussed above. Anderson et al also teach the hydroxyl groups are 5' OH groups of nucleoside polymers deblocked by the detritylation step (column 19, line 40-column 20, line 50). Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the hydroxyl groups are 5' OH groups of nucleoside polymers deblocked by the detritylation step

Regarding claim 49, the method of claim 29 is discussed above. Gamble et al teach the block nucleoside monomer is deposited at the location by pulse jetting; namely, micro-sized spots of reagents are dispensed in particular locations (column 3, lines 35-45) by pulse jetting (column 9, lines 50-65).

Regarding claim 50, the method of claim 28 is discussed above. Gamble et al teach the blocking group is a trityl group (column 2, lines 25-35), which is an acid labile group. In addition, Anderson et al also teach the blocking group is a trityl group (column 19, line 40-column 20, line 50), which is an acid labile group, and the deblocking fluid comprises dichloroacetic acid (step i of Table I). Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the blocking group is a trityl group which is deblocked with an acid.

Regarding claim 54, the method of claim 28 is discussed above. Anderson et al also teach the deblocking fluid comprises an organic solvent; namely, acetonitrile (column 13, line 67-column 14, line 1). The vapor pressure of acetonitrile at 0^{o}C and 1 ATM pressure is 24.75 mm Hg, which is 3.3 kPa. Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the deblocking fluid comprises an organic solvent having the required vapor pressure.

Regarding claim 55, the method of claim 28 is discussed above. Anderson et al also teach contacting the substrate comprising the attached blocked nucleoside polymer with an oxidation fluid prior to contacting with the deblocking fluid; namely, oxidation of an added nucleoside is performed before the sequential addition of the next monomer (Table I, step iv). Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the substrate comprising the attached blocked nucleoside

polymer is contacted with an oxidation fluid prior to contacting with the deblocking fluid.

Regarding claim 56, Gamble et al teach a method of synthesizing an addressable array of at least two different oligonucleotides of differing monomeric sequence bonded to different known locations on a substrate. In a single exemplary embodiment, Gamble et al teach a substrate upon which micro-sized spots of reagents are dispensed in particular locations (i.e., first and second locations; column 3, lines 35-45). The reagents are removable from the substrate surface (column 2, lines 45-50), and thus are attached to the surface. The reagents are phosphoramidites (column 2, lines 13-16), which are blocked nucleoside monomers in accordance with the example presented in the first paragraph on page 15 of the instant specification. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "blocked nucleoside monomer." Because the spotted blocked nucleoside monomers are localized onto specific locations on the substrate (column 2, lines 15-25), and because the locations are predetermined by a used prior to synthesis of the array (column 2, lines 39-45), the array is an addressable array in accordance with the example presented on page 10 of the instant specification. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding an "addressable array." The monomers are deblocked by deprotecting reagents to remove a trityl protecting group that blocks further synthesis on the nucleoside monomer (column 4, lines 35-45 and column 12, lines 59-67). The deblocking

unmasks functional groups on the attached unblocked nucleoside on the surface which are then reacted with another blocked nucleoside monomer to produce the addressable array of nucleic acid molecules on the surface; namely, the next blocked phosphoramidite molecule is applied (column 13, lines 15-30).

Gamble et al teach additional reagents are transported to a reaction chamber which contacts the substrate, wherein the additional reagents include deprotecting reagents (column 4, lines 35-45). The deprotecting reagent is a deblocking agent because it removes a trityl protecting group that blocks further synthesis on the nucleoside monomer (column 12, lines 59-67). The deblocking fluid is then displaced from the surface of the substrate, which now comprises attached unblocked nucleoside monomers at first and second locations, using a purging fluid in the form of a wash fluid used between synthesis steps (column 10, lines 15-25). Each spot on the array (i.e., location) has a unique sequence (column 12, lines 30-40); thus, there are at least two different oligonucleotides of differing monomeric sequence bonded to different known locations on the surface of the array.

It is noted that while the claim is drawn to contacting the "entirety" of "said surface displaying bound blocked monomers," the claim does not specifically require contacting the **entire** surface of the substrate; i.e., the word "entirety" is interpreted as referring only to "said surface displaying bound blocked monomers," which is merely the portion of the substrate having the blocked monomers, but not necessarily the remainder of the entire surface of the substrate which does not display the blocked monomers. Thus, the claim

encompasses contacting only the portion of the surface of the substrate having the first and second locations comprising the monomers manipulated by the method.

Gamble et al teach the addition of reagents to the surface of the substrate that is sealed in a reaction chamber in several different configurations.

In a first embodiment, the substrate is sealed in a reaction chamber in which reagents flow over and immerse the substrate (column 3, lines 35-60), such that the entire surface of the substrate is uniformly covered with reagents (column 6, lines 35-40). The online dictionary at dictionary.cambridge.org defines "immerse" as "to put something or someone completely under the surface of a liquid." Thus, "immersion" of the substrate contacts the reagents with the entirety of the surface displaying the bound blocked monomers. Thus, Gamble et al clearly suggest uniformly covering (i.e., contacting) the entirety of the surface displaying the bound blocked monomers (column 6, lines 35-40).

In a second embodiment, Gamble et al also teach Figures 4a-c and 5, which show substrate 20 pressed against chamber 26 and against seal 28, which defines the surface of the substrate subjected to the fluid treatments (column 6, lines 30-45 and column 7, lines 25-40).

In a third embodiment, Gamble et al teach single array 66, which comprises a plurality of blocked phosphoramidites (column 2, lines 13-50), is pressed against the seal and subjected to reagent flow (i.e., a reagent stream; Figure 4c and column 7, lines 1-20).

Thus, in comparing the second embodiment of Figure 4a to the third embodiment of Figure 4c, it is clear that Figure 4a encompasses containing all of the spots on the array within seal 28 so that the entirety of the surface displaying the bound blocked monomers is contacted with the reagents that are flowed through the reaction chamber.

Alternatively, Figure 4c clearly indicates that at least one array, which is the entirety of the surface displaying the bound blocked monomers, is within seal 28 so that the entirety of the surface displaying the bound blocked monomers is contacted with the reagents flowed through the reaction chamber. The additional arrays 66 of Figure 4c are other structures encompassed by the open claim language "comprising" of the instant claims.

In addition, as noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Thus, the teaching of Gamble et al that an individual array within a plurality of arrays **may** be sealed against the reaction chamber separately (column 7, lines 1-15) encompasses the alternate embodiment wherein the individual arrays are **not** separately sealed against the chamber; i.e., all of the arrays are sealed against the chamber at the same time (compare Figures 4a and 4c).

Therefore, in each of the embodiments detailed above, the portion of substrate 20 contained within seal 28 is interpreted as "the entirety of the surface displaying the bound blocked monomers," and because the entire surface of the substrate within seal 28 is contacted with the reagents as described below,

Gamble et al teach contacting "an" entire surface of said substrate with reagents as required by the claim.

While Gamble et al teach the claimed entirety of the surface is contacted with the claimed fluids by contacting with a reaction chamber wherein reagents flow over and immerse the substrate (column 3, line 45-column 4, line 5), and that the reagents include phosphoramidites (i.e., blocked nucleoside monomers), wash reagents, deprotection (i.e. deblocking) reagents, activation reagents, oxidation regents, and any other necessary synthesis reagents (column 4, lines 35-46), Gamble et al do not explicitly teach the wash reagent contacts the entire surface of the substrate.

However, Anderson et al teach a method for producing an array of oligonucleotides on a substrate, wherein a first nucleoside capped with a trityl group attached to the surface of a support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, a surface of the substrate (i.e., solid support) is exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20). Anderson et al also teach

increased washing efficiency and quantitative replacement of one reagent by the next is a fixed requirement for polymer synthesis on a surface (column 19, lines 25-40), and that extensive washing between use of reagents is necessary to ensure each reagent reacts properly so that the yield of the polymer is not diminished (column 3, lines 45-60). Anderson et al also teach the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract). Thus, Anderson et al teach the known technique of performing all of the fluid steps, including washing, with a single reaction chamber.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising steps including washing of the array substrate as taught by Gamble et al so that each previous reagent is quantitatively replaced by a washing fluid as taught by Anderson et al and so that the reaction chamber of Gamble et al is used as a single reaction chamber for all of the fluid manipulation steps as taught by Anderson et al arrive at the instantly claimed method with a reasonable expectation of success. Quantitative replacement of reagents on the surface of the support requires displacement of said reagent from the entire surface of the substrate via use of the washing fluid as taught by Anderson et al. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of ensuring that each reagent reacts properly so that the yield of the polymer is not diminished, thus meeting the fixed requirements of washing efficiency and

quantitative replacement of solutions during polymer synthesis as explicitly taught by Anderson et al (column 19, lines 25-40 and column 3, lines 45-60). The ordinary artisan would also have been motivated to use the single reaction chamber of Anderson et al as a single reaction chamber for all of the fluid steps in the method of Gamble et al because the use of a single reaction chamber for all of the fluid steps, including washing, would have resulted in a method having the additional added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow as explicitly taught by Anderson et al (Abstract). In addition, it would have been obvious to a person of ordinary skill in that art at the time the claimed invention was made that the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al could have been applied to the method of Gamble et al with predictably results because the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al predictably results in a reliable method of performing DNA synthesis steps.

Regarding claim 33, the method of claim 56 is discussed above. Gamble et al teach the substrate comprises a surface of a support containable within a flow cell; namely, the substrate is a slide (column 3, lines 5-10 and substrate 20 of Figure 1), which is capable of being contained within a flow cell.

Alternatively, Anderson et al also teach the substrate comprises a surface of a support containable within a flow cell; namely, the substrate (i.e., reaction media) is in the internal space of a hollow enclosure (column 5, lines 20-38),

which is a flow cell. A review of the specification yields no limiting definition of a "flow cell;" thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "flow cell." Thus, modification of the method of Gamble et al with the teachings of Anderson et al a results in a method wherein the substrate comprises a surface of a support containable within a flow cell.

In addition, it is noted that while the support is required to be containable within a flow cell, the claim does not require an active method step wherein the substrate is actually placed within a flow cell.

Regarding claim 57, the method of claim 56 is discussed above. Gamble et al teach the at least two oligonucleotides comprise the same sequence; namely, the method produces an array (Abstract) of oligonucleotides (column 2, lines 35-50) by jetting the reagents used to make the array (Abstract). Because Gamble teach each jet of a plurality of jets has the same reagent sent to it (column 6, lines 10-15), each jetted position comprises the same sequences.

In addition, Anderson et al also teach the at least two oligonucleotides comprise the same sequence; namely, the solutions are added to the support in a chamber (i.e., rotor; column 20, lines 55-65), which is interpreted as a single synthesis on a single support, thereby producing one full length sequence at more than one location on the support. Thus, modification of the method of Gamble et al with the teachings of Anderson et al results in a method wherein the at least two oligonucleotide comprise the same sequence composition.

Regarding claim 58, the method of claim 56 is discussed above. Gamble et al also teach the at least two oligonucleotides comprise the different sequence compositions; namely, the method produces an array (Abstract), wherein the arrays provide a large number of different compounds in a small space (column 1, lines 1-10), and the compounds are different oligonucleotides (column 2, lines 35-50).

Regarding claim 59, the method of claim 26 is discussed above. While neither Gamble et al nor Anderson et al explicitly teach oxidation before deblocking, the courts have held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C.

Regarding claim 61, the method of claim 28 is discussed above. Anderson et al also teach the substrate is planar; namely, the membrane is a flat disk (column 6, lines 49-56).

6. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) in view of Anderson et al (U.S. Patent No 5,186,824, issued 16 February 1993) as evidenced by the online dictionary at dictionary.cambridge.org as applied to claim 28 above, and further in view of Greene et al (*Protective Groups in Organic Synthesis*, 3rd ed., Wiley and Sons, New York, 1999, page 106).

Regarding claim 37, the method of claim 28 is discussed above in Section 5.

Neither Gamble et al nor Anderson et al explicitly teach the purging fluid density is higher than the deblocking fluid density.

However, Green et al teach the deblocking (i.e., cleavage) of dimethoxytrityl (i.e., trityl) groups of deoxyribonucleotides using 3% trichloroacetic acid (density 1.62 g/mL) in 95:5 nitromethane/methanol (densities 1.127 and 0.791 g/mL, respectively), with the added advantage that the mixture reduces the levels of depurination of the reaction product (page 106). Depurination results in a degraded product on the array.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). In the instant case, the solvent mixture is predominantly nitromethane, with a density of 1.127 g/mL, with 5% methanol, having a lower density. A final concentration of 3% of the higher density trichloroacetic acid is believed to produce a solution with an overall density nearly equal to that of nitro methane, because similar percentages of both a higher density liquid and a lower density liquid are added. Thus, the final density of the solution of Greene et al is believed to be lower that 1.325 g/mL, which is the density of the purging fluid of

Anderson et al. Thus, Greene et al teach the known technique of having a purging fluid density that is higher than the deblocking fluid density.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Gamble et al in view of Anderson et al so that the deblocking solution is the deblocking solution of lower density as taught by Greene et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of having fewer degraded products on the array via a reduction in the levels of depurination of the reaction product as explicitly taught by Greene et al (page 106). In addition, it would have been obvious to the ordinary artisan that the known technique of using the purging fluid density of Greene et al could have been applied to the method of Gamble et al in view of Anderson et al with predictable results because the purging fluid density of Greene et al predictably results in reliable purging of the array.

7. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) in view of Anderson et al (U.S. Patent No 5,186,824, issued 16 February 1993) as evidenced by the online dictionary at dictionary.cambridge.org as applied to claims 28 and 44 above, and further in view of Mian et al (U.S. Patent No. 6,319,469, issued 20 November 2001).

Regarding claim 45, the method of claims 28 and 44 is discussed above in Section 5.

While neither Gamble et al nor Anderson et al explicitly teach specific flow rates, Anderson et al do teach the method wherein the flow rate is controlled and monitored during passage of reagents (column 5,lines 25-27 and column 14, lines 44-53 21). Anderson et al further teach that it is advantageous to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (column 21, lines 30-65). Thus, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step.

In addition, Mian et al teach a method of synthesizing oligonucleotides on a disc (Figure 23b and column 5, lines 65-67), wherein the flow rates are from about 1 cm/sec to about 20 cm/sec having the added advantage that variable flow rates within the claimed range allow fluid transfer over a wide range of times scales as required by the various processes (column 12, lines 40-57). Thus, Mian et al teach the known technique of using the instantly claimed flow rates.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the flow rates of the method of Gamble et al in view of Anderson et al with the range of flow rates as taught by Mian et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of having flow rates that allow fluid transfer over a wide range of times scales as required by the various processes as explicitly taught by Mian et al (column 12, lines 40-57). In addition, it would have been obvious to the ordinary artisan that the known technique of using the range of flow rates as taught by Mian et al could have been applied to the method of Gamble et al inv view of Anderson et al with predictable results because the range of flow rates as taught by Mian et al predictably results in flow rates suitable for the synthesis of oligonucleotides on an array.

8. Claims 48, 51, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) in view of Anderson et al (U.S. Patent No 5,186,824, issued 16 February 1993) as evidenced by the online dictionary at dictionary.cambridge.org as applied to claims 28, 33,and 56 above, and further in view of Bass et al (U.S. Patent Application Publication No. US 2003/0003222 A1, published 2 January 2003).

Regarding claims 48 and 51, the method of claims 28, 33, and 56 is discussed above.

Gamble et al teach the fluids enter and exit reaction chamber 26 through the fluid inlet and fluid outlet (i.e., ports 32 and 34 (i.e., claim 51; Figures 4a-c and column 5, lines 55-65). Anderson et al also teach the synthesis steps are done on a substrate (i.e., a flat disk; column 6, lines 49-60) in a flow cell in the form of a rotor chamber (Figure 1 and Abstract), which comprises a fluid inlet in the form of the opening of fluid line 100 and a fluid outlet in the form of the opening of fluid line 102 (Figure 1 and column 12, lines 20-30).

Thus, while Gamble et al and Anderson et al both teach fluid inlets and outlets, and while Anderson et al teach the synthesis is done in the flow cell, the references do not explicitly teach the jetted substrate of Gamble et al is placed within a flow cell for the displacing step (i.e., purging; claim 48) or the deblocking step (i.e., claim 51).

However, Bass et al teach the manufacturing of biopolymer arrays (Abstract), wherein nucleotide monomers are jetted on a substrate, followed by placement of the substrate into a flow cell having a fluid inlet and a fluid outlet (i.e., claim 51; paragraphs 0038 and 0045), and wherein purging fluids in the form of washing fluids are added to the substrate within the flow cell (i.e., claim 48; paragraph 0051) and deblocking agents are added to the substrate in the flow cell (i.e., claim 51; paragraph 0052). Bass et al also teach the use of the flow cell for the synthesis steps has the added advantage of allowing the determination of the level of contaminants in the fluids exiting the flow cells

(paragraph 0047). Thus, Bass et al teach the known technique of placing a jetted substrate within a flow cell for the displacing step (i.e., purging; claim 48) or the deblocking step (i.e., claim 51).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of flow cells comprising inlets and outlets as taught by Gamble et al in view of Anderson et al so that the jetted substrate is placed within a flow cell for the displacing step (i.e., purging; claim 48) or the deblocking step (i.e., claim 51) as taught by Bass et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of allowing determination of the level of contaminants in the fluids exiting the flow cells as explicitly taught by Bass et al(paragraph 0047). In addition, it would have been obvious to the ordinary artisan that the known technique of jetted substrate within a flow cell for the displacing step or the deblocking step as taught by Bass et al could have been applied to the method of Gamble et al in view of Anderson et al with predictable results because the known technique of jetted substrate within a flow cell for the displacing step or the deblocking step as taught by Bass et al predictably results in the reliable synthesis of oligonucleotides on a substrate surface.

Regarding claim 52, the method of claim 51 is discussed above. Gamble et al teach reaction chamber 26, which is a flow cell because fluids flow through

it, is oriented vertically (Figure 5). Further, Anderson et al teach the flow cell (i.e., rotor) is oriented vertically (Abstract). In addition, Bass et al also teach the support is introduced into the flow cell vertically (paragraph 0059); thus, the flow cell has at least one portion oriented vertically. Therefore, modification f the method of Gamble et al with the teachings of Anderson et al and Bass et al results in a vertically oriented flow cell.

9. Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) in view of Anderson et al (U.S. Patent No 5,186,824, issued 16 February 1993) as evidenced by the online dictionary at dictionary.cambridge.org as applied to claims 28 and 44 above, and further in view of Farr (U.S. Patent No. 3,969,250, issued 13 July 1976).

Regarding claim 53, the method of claims 28 and 44 is discussed above in Section 5.

Neither Gamble et al nor Anderson et al teach a pressure gradient.

However, Farr teaches stratification of liquids using a pressure gradient; namely, creation of supernatant fluid by centrifuging immiscible liquids (column 1, lines 5-10), which is in accordance with the statement on 33 of the instant specification that centrifugal acceleration is used to generate pressure gradients. Farr also teaches the stratification created by the pressure gradient has the added advantage of eliminating the need for decanting, thereby minimizing labor

and possible contamination of the sample (column 2, lines 24-26). Thus, Farr teaches the known technique of using a pressure gradient.

It would therefore have been obvious to a person or ordinary skill in the art at the time the claimed invention was made to have modified the method comprising using a stratified interface as taught by Gamble et al in view of Anderson et al so that the stratified interface is achieved using a pressure gradient as taught by Farr to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of minimizing labor and possible contamination of the sample as explicitly taught by Farr (column 2, lines 24-26). In addition, it would have been obvious to the ordinary artisan that the known technique of using the pressure gradient of Farr could have been applied to the method of Gamble et al in view of Anderson et al with predictable results because the pressure gradient of Farr predictably results in reliable method of stratifying fluids.

Response to Arguments

10. Applicant's arguments with respect to the previous rejections of the claims have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

Conclusion

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

13. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1634

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